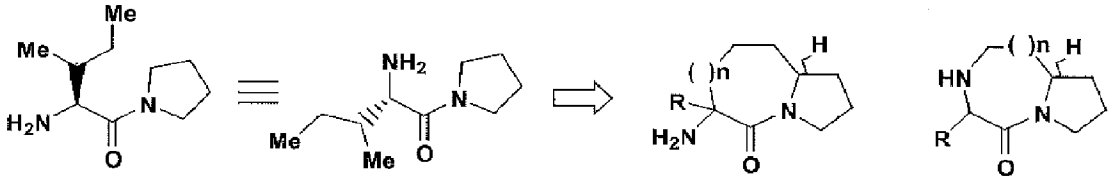
Chem Sig Events **April 26, 1999**

Executive Summary: Nothing to report

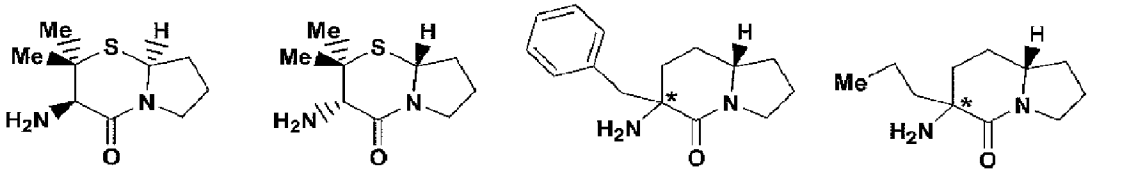
Competitive Update: No new developments.

The goal of the program is to discover small molecule inhibitors of dipeptidyl peptidase IV (DP-4) for use in the treatment and prevention of diabetes. Inhibition of DP-4 should prevent the degradation of GLP-1 and potentiate its actions in vivo. We have been working to identify novel and proprietary conformationally restricted dipeptide scaffolds which would mimic the binding interaction of the known DP4 inhibitor BMS-326430 (Ile-Pyrrolidide). Since this inhibitor can adopt a variety of configurations (two of which are shown below), emphasis has been placed towards generating lactams A and B which differ in their placement of the key pharmacophores required for binding to the enzyme.



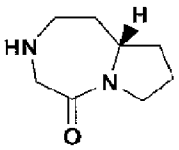
BMS-326430 A B

Full automation of the assay has now been completed utilizing purified pig kidney DP4 (inhibitor/enzyme preincubation time of 5 minutes). In the "exo" amino bicyclic series (generic structure A), four new compounds which attempted to incorporate a requisite hydrophobic group in the scaffold (geminal dimethyl for BMS-345588 and BMS-346476, benzyl for BMS-345698/BMS-345699, and propyl for BMS-345623) were assayed. None of the compounds elicited significant inhibition at 10 uM. Based on recent modeling results performed by the Macromolecular Structure Group, future emphasis will be placed in generating the related bicyclic azocine (8,5-fused ring structure) which should better adopt the low energy conformation of BMS-326430.

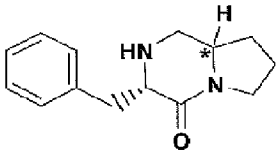


BMS-345588 **BMS-346476** **BMS-345698 (Isomer A at *) BMS-345699 (Isomer B at *)** **BMS-345623 (single isomer at *)**

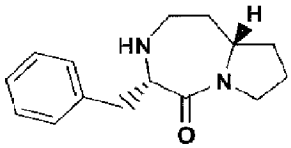
In our last report it was stated that the "endo" amino bicyclic compound BMS-309909 exhibited significant inhibition of human DP4 at 10 uM upon 30 min incubation with the enzyme. Recent testing of this compound versus the pig kidney enzyme showed no inhibition with this compound. A retest versus human DP4 will be performed once additional enzyme is available. The 6,5-fused compound BMS-344554 and the 7,5-fused compounds BMS-346575 and BMS-346587, designed to incorporate a requisite hydrophobic interaction in the molecules, were inactive against pig kidney DP4. Again, based on modeling results, future emphasis will be placed on generating the related 8,5-fused systems with special emphasis on the effect of stereochemistry at the bridgehead center.



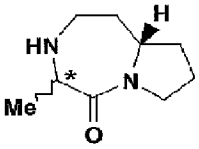
BMS-339909



BMS-344554
(10:1 mixture at *)



BMS-346575



BMS-346587
(1:1 mixture at *)